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Original Research Article

Evaluation and Selection of Gel Base for the Formulation of Dexpanthenol Products

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Abstract

Purpose: *To formulate dexpanthenol gels with enhanced in vivo absorption properties via skin.*
Methods: *Carboxyvinyl derivatives (Carbopol 980 and Ultrez 10) and poloxamer (Lutrol F 127) were used as the hydrogel base in the formulations. Changes in rheological properties (apparent viscosity and penetration values) during the storage period were examined by Rheotest RN rotational viscometer and PNR12 penetrometer. In vitro release study using Franz diffusion cell was employed to compare the release characteristics of the formulated hydrogels with those of a reference cream.*
Results: *The flow curves of the gels with Carbopol 980 and Ultrez 10 showed pseudoplastic flow. Lutrol F 127 gels presented thixotropic behaviour. The consistency of the studied gels was in the following rank order: Lutrol F 127 > Ultrez 10 > Carbopol 980. In vitro results showed that dexpanthenol was released in lower amounts from the reference cream than from the three test gels. No significant differences were observed in the amount of active substance released from the gels due probably to the fact that Carbopol 980 and Ultrez 10 are both carboxyvinyl polymers. The highest amount of dexpanthenol was released from Lutrol F 127 gel.*
Conclusion: *The hydrogel made with Lutrol F 127 gel base possesses the best properties of all the gels and is recommended for the formulation of a suitable dexpanthenol gel.*

Keywords: *Hydrogel, Dexpanthenol, Carboxyvinyl polymers, Gels, Carbopol, Poloxamer, Rheology, Drug release, Penetrometer*

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INTRODUCTION

Hydrogels are aqueous semisolid preparations made comprising macromolecules dispersed in large amounts of water. Hydrogels are favoured for the treatment of dermatological diseases, and delivery of drugs through skin as well as for mucosal applications due to their rheological properties [1,2]. A large number of macromolecular substances can be used as a gel base [3-5]. The dispersion of active ingredient in the gel base depends on the physicochemical properties of the macromolecular substances, such as molecular weight and viscosity.

Dexpanthenol is a water-soluble substance used for the treatment and prevention of skin disorders as well as for skin protection [6-12]. At present only ointments, creams and solutions containing dexpanthenol are available in the pharmaceutical market for external use.

The aim of this study was to formulate dexpanthenol gels and to select the one which has the best rheological and drug release properties using *in vitro* studies.

EXPERIMENTAL

Materials

Dexpanthenol working standard (BASF), Carbopol 980 (Lubrizol) Lutrol E 400 (BASF), Lutrol F127 (BASF), Ultrez 10 (Lubrizol), triethanolamine (TEA, Merck), liquid paraffin (Sigma-Aldrich), and methylparaben/propyl-paraben mixtures were used in this study.

Formulation of carbopol gels with dexpanthenol

Carbopol 980 and Ultrez 10 were separately dispersed in a solution of methylparaben and propylparaben. Carbopol 980 was left for approximately 50 min, while Ultrez kept for < 10 min to achieve hydration. The dispersions had a low viscosity with cloudy appearance. The cloudy solution was neutralized with triethanolamine to achieve the desired pH. The mixtures were homogenized using a multifunctional laboratory mixer. Since dexpanthenol is soluble in water, it was easily incorporated in carboxivinyl gel bases.

Formulation of Lutrol F 127 gel with dexpanthenol

Dexpanthenol was dissolved in the mixture of Lutrol E 400, distilled water and liquid paraffin, then mixed on a water bath at 60 - 70 ^{o}C. Lutrol E 400 was a viscosity modifier. To this solution was added slowly Lutrol F 127, continuously stirring it until it dissolved. The mixture was cooled to room temperature and homogenized using a mixer until the air bubbles disappeared, resulting in a homogeneous white gel. Table 1 shows the composition of the hydrogel preparations.

Rheological stability study

The rheological characteristics of the pharmaceutical forms were measured with a Rheotest RN rotational viscometer (Medingen GmbH) and a PNR12 penetrometer (Anton Paar). Measurements were made three times, once after preparation, once after 50 days and finally once after 100 days. Gels were kept for storage period in plastic boxes, in tightly closed containers at 2 - 8 °C in a refrigerator.

In vitro release study

In this study, a Franz diffusion cell (Pharma Alliance), equipped with a cellulose acetate dialysis membrane which separated the donor phase (gel) and acceptor compartment (distilled water), was positioned in a temperature controlled water-bath at 37 ± 0.5 ^{o}C.

The quantity of the drug that diffused from the gel was determined using high performance liquid chromatographic (HPLC) method [13,14]. The Agilent HPLC instrument was equipped with a Luna C18, 150 × 4.6 mm, 3 µm (Phenomenex) column as stationary phase. The mobile phase consisted of formic acid-methanol in a ratio of 80: 20 while the flow rate was 0.8 mL/min, column temperature set to 40 ^{o}C, and the injection volume 10 µL. The detection wavelength was 205 nm.

Statistical analysis

Rheological and release results are presented as ± standard deviation (SD), and Microsoft Excel ver. 2003 was used for the computation. Hysteresis rate was computed using Origin 8 software (OriginLab Corporation).

RESULTS

Rheological profile

Figures 1, 2 and 3 show the flow curves of dexpanthenol gels formulated with Carbopol 980 and Ultrez 10 immediately after preparation, and after 50 and 100 days storage, respectively. Figure 4 shows the flow curves of dexpanthenol gel prepared with Lutrol F 127 after preparation. Analysis of the flow curves after storage for 50

Table 1: Composition of the formulated gels

Ingredient	Carbopol 980 gel (g)	Ultrez 10 gel (g)	Lutrol F 127 gel (g)
Dexpanthenol	5	5	5
Carbopol 980	1	-	-
Ultrez 10	-	1	-
TEA	0,7	1	-
Paraben solution	ad 100	ad 100	-
Paraffin oil	-	-	10
Lutrol E 400	-	-	15
Lutrol F 127	-	-	18
Distilled water	-	-	52

and 100 days shows clearly that pseudoplastic and thixotrophic flow, which are characteristic of Carbopol and Lutrol F 127 gels, respectively, remained unchanged.

The rheological characteristics of hydrogels are typified by very slight variation in apparent viscosity and hysteresis rate (Tables 2 and 3).

The measurement of gel consistency by penetrometer is an official method in the European Pharmacopoeia. The penetration curves of the studied gels, measured directly for the fresh preparation and after 50 days of storage, are presented in Tables 4 and 5.

The *in vitro* release profiles of Dexpanthenol from the test gels and reference cream are presented in Figure 7.

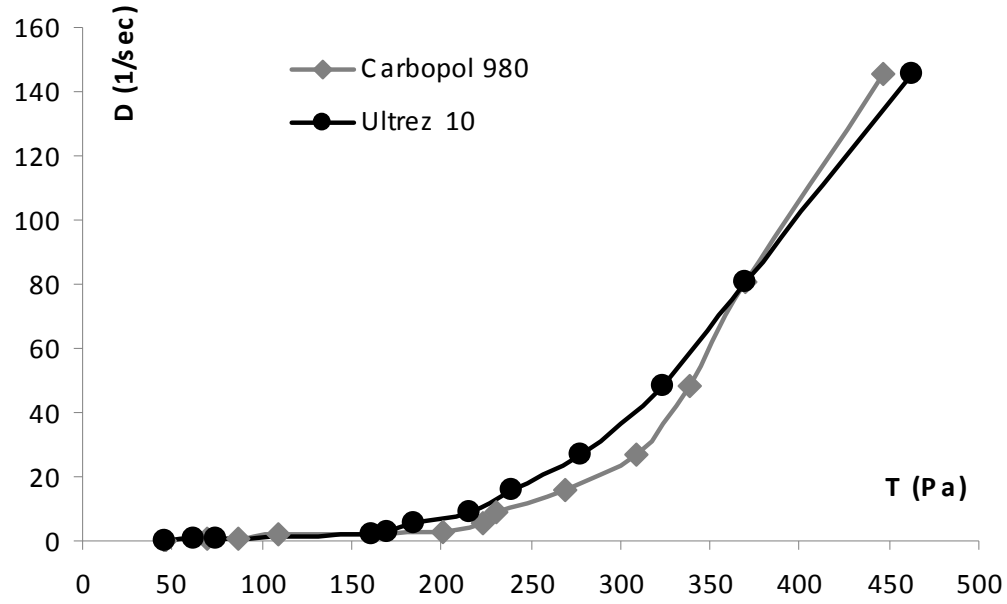

Figure 1: Flow curves of Carbopol gels after preparation (n = 3)

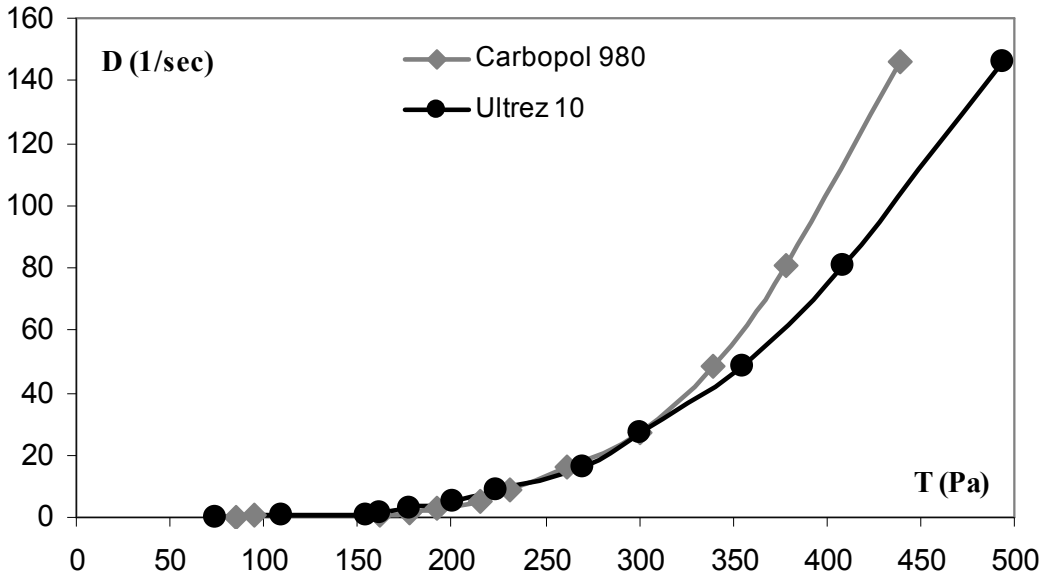

Figure 2: Flow curves of Carbopol gels after 50 days storage (n = 3)

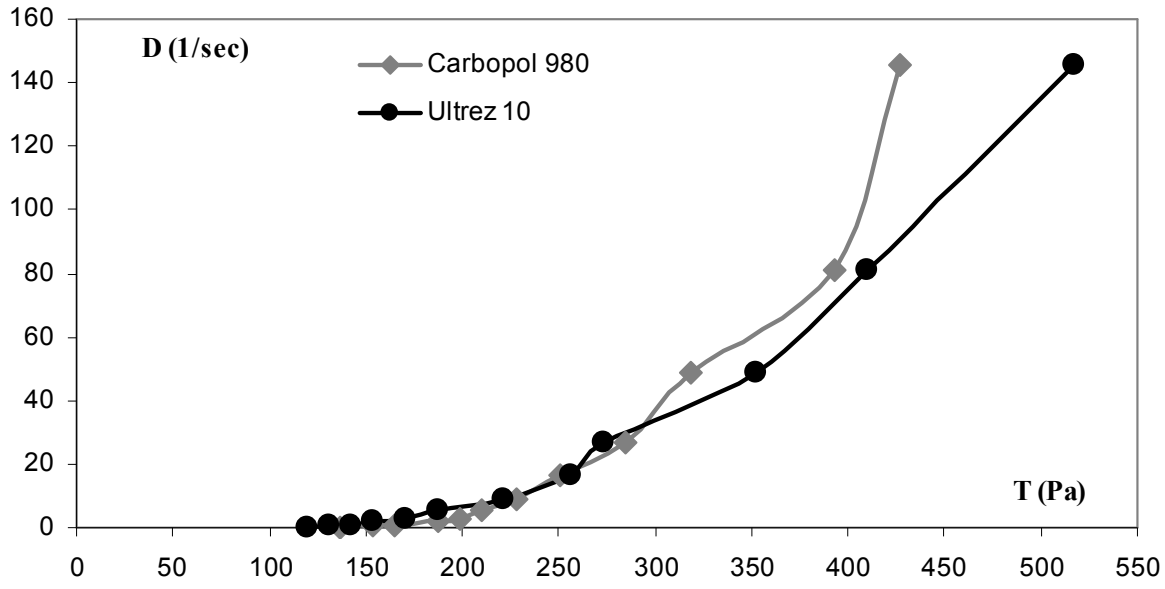

Figure 3: Flow curves of Carbopol gels after 100 days storage (n = 3)

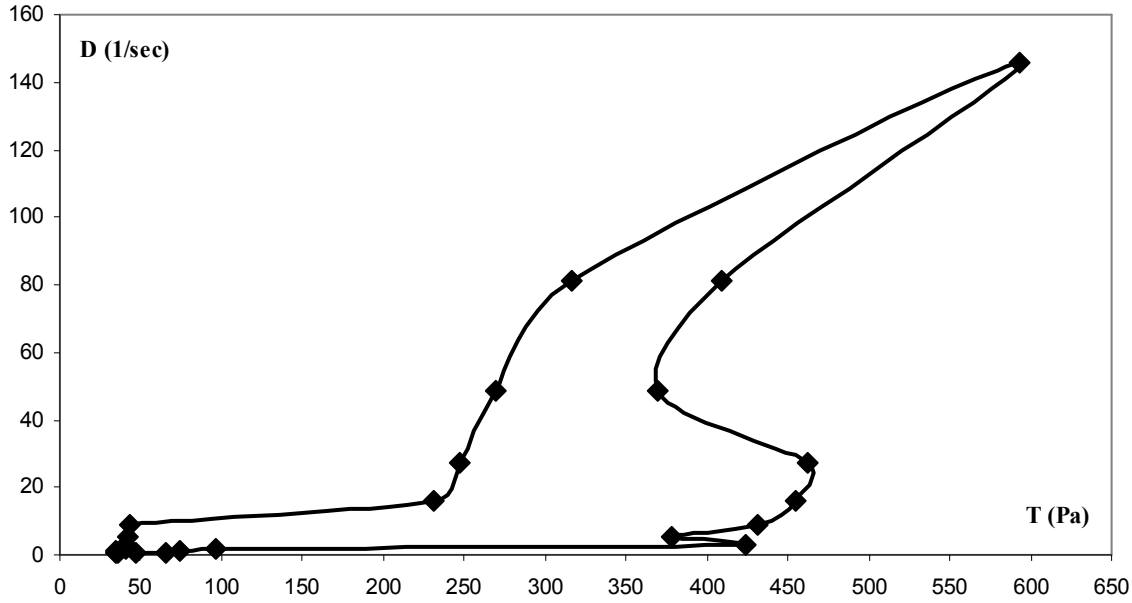

Figure 4: Flow curve of dexpanthenol gel prepared with Lutrol F 127 (n = 3)

Table 2: Apparent viscosity of the hydrogels (shear rate, D = 48, 6 1/s)

Storage period	Gel viscosity (Pa.s ± SD)	
	Carbopol 980	Ultrez 10
Freshly prepared	6.98 ± 0.11	6.66 ± 0.54
After 50 days	6.98 ± 0.21	7.30 ± 0.09
After 100 days	6.09 ± 0.34	7.26 ± 0.18

Table 3: The extent of hysteresis for dexpanthenol gels with Lutrol 127

Storage period	Hysteresis rate (Pa. 1/s± SD)
Freshly preparation	16599.49 ± 112.2
After 50 days	16632.23 ± 219.7
After 100 days	16612.55 ± 109.5

Table 4: Penetration values for test fresh gels

Time(s)	Penetration value (mm ± SD)		
	Lutrol F 127 gel	Ultrez 10 gel	Carbopol 980 gel
0	0	0	0
15	9.80 ± 0.02	11.00 ± 0.01	12.00 ± 0.01
20	10.00 ± 0.01	15.00 ± 0.01	13.30 ± 0.02
30	12.00 ± 0.02	17.00 ± 0.01	18.93 ± 0.02
40	13.06 ± 0.02	18.00 ± 0.01	23.00 ± 0.01
50	14.40 ± 0.01	20.00 ± 0.01	24.60 ± 0.02
60	15.00 ± 0.01	23.00 ± 0.01	26.00 ± 0.01

Table 5: Penetration values for test gels after 50 days of storage

Time(s)	Penetration value (mm ± SD)		
	Lutrol F 127 gel	Ultrez 10 gel	Carbopol 980 gel
0	0	0	0
15	11.00 ± 0.01	20.00 ± 0.01	19.70 ± 0.01
20	11.00 ± 0.01	21.40 ± 0.02	20.80 ± 0.01
30	11.80 ± 0.01	23.20 ± 0.02	23.30 ± 0.01
40	12.80 ± 0.02	24.80 ± 0.01	25.20 ± 0.02
50	13.70 ± 0.02	26.20 ± 0.02	26.00 ± 0.02
60	14.60 ± 0.02	26.50 ± 0.02	26.70 ± 0.01

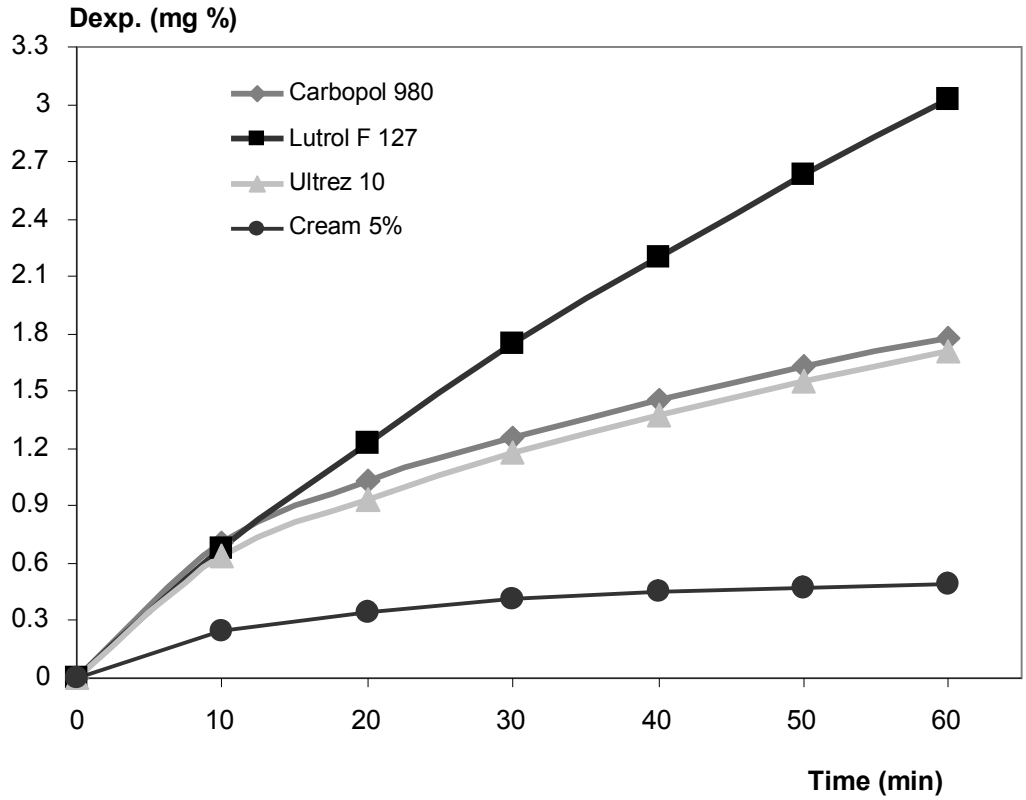

Figure 7: Release profile of dexpanthenol from the studied gels and pharmaceutical cream

DISCUSSION

Rheological tests usually give accurate data on the stability, extent of deformation and flow properties of gels. The flow curves of with Carbopol 980 and Ultrez 10 gels indicate pseudoplastic flow while Lutrol F 127 gels exhibited thixotrophic behaviour, with the "up-flow curve" not directly overlapping the "down-curve". The measure of thixotropy is the closed area between these two curves. The consistency of the test gels followed rank order: Carbopol 980 < Ultrez 10 < Lutrol F 127 gel.

In vitro drug release rate was lowest amount from the reference cream, compared with the test gels. Reports on studies of commercially available dexpanthenol creams were not

available to the authors, but it is known generally that active substance release is better from hydrogels than from creams [15,16]. Carbopol 980 and Ultrez 10, which are both carboxyvinyl polymers, demonstrated similar drug release rates. Among the three test gels dexpanthenol was released fastest from the Lutrol F 127 gel.

The gel containing 5 % dexpanthenol and formulated with Lutrol F 127 exhibited the most suitable characteristics, namely, thixotropic behaviour, consistency and most rapid drug release.

CONCLUSION

The findings of this study demonstrate that dexpanthenol gels with higher absorption into skin than commercially available creams of the drug are feasible. In this regard, dexpanthenol gels formulated with Lutrol F 127 appears to be suitable for production on an industrial scale.

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